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Involuntary treatment of schizophrenia patients 2004–2010 in Denmark

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Andersen TH, Kappers D, Sneider B, Uggerby P, Nielsen J. Involuntary treatment of schizophrenia patients 2004-2010 in Denmark.

Objective: Treatment of schizophrenia is frequently complicated by patients' ambivalence and lack of insight into the disease, occasionally warranting involuntary treatment. This study aims to describe involuntary treatment in Danish schizophrenia patients.
Method: Patients diagnosed with a lifetime ICD-10 F20 schizophrenia diagnosis and alive in the period 2004–2010 were identified in the Danish Psychiatric Central Research Register, and data were linked to The Registry of Coercive Measures in Psychiatric Treatment.
Results: Within the study period, a total of 18 599 admitted patients were identified, 3078 of which underwent involuntary treatment. The incidence rate for any involuntary treatment was 2.1 per in-patient year and 1.7 and 0.3 per in-patient year for rapid tranquilization and involuntary treatments, respectively. Somatic diseases comprised 34.5% of all involuntary treatments. Psychotropics comprised 56.9% with antipsychotics as the most common drug class (99.5%). Olanzapine was the most commonly used antipsychotic drug (33.2%). Treatment with depot injection and clozapine comprised only 13% and 4.8% of the antipsychotics used, respectively. Electroconvulsive therapy comprised 4.8% of all involuntary treatment.
Conclusion: Involuntary treatment involved a wide range of somatic treatment. Antipsychotic medicine was the most common psychotropic used. Involuntary treatment with depot antipsychotics and clozapine were rare.

Key words: schizophrenia; involuntary treatment; antipsychotic; clozapine; ECT

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Significant outcomes

- One-third of all involuntary treatments included somatic treatment or procedures, with treatment of acetaminophen overdose and compulsory feeding as the most common.
- Schizophrenia patients only rarely are subjected to involuntary treatment with clozapine or depot antipsychotics.
- Patients subjected to involuntary treatment had a history of more psychiatric admissions and an earlier onset of schizophrenia.

Limitations

- The mental health acts differ between countries, and therefore, the conclusions of this study may not be generalizable.
- Description of symptoms or indication for the involuntary treatment was not available.
- Data from The Registry of Coercive Measures in Psychiatric Treatment were only available from 2004 until end of 2010.

Introduction

Schizophrenia is a debilitating and social disruptive disease affecting 0.5–1.0% of the population and often it have a chronic course with 10% being institutionalized (1–3). Besides being tormented by psychotic symptoms, schizophrenia patients more often live alone (4) and are having comorbid substance misuse (5).

In addition schizophrenia is a life-shortening disease with up to 25 years reduction of lifespan compared with the background population (6). Lifetime risk for committing suicide is approximately 5% (7). Lifestyle related conditions such as inactivity, obesity, smoking contribute significantly to increased mortality causing increased risk of cardiovascular diseases (8). Studies also have shown that schizophrenia patients are less likely to receive the proper somatic treatment (9).

Antipsychotics are considered the cornerstone in treatment, but patients' ambivalence and lack of insight often tend to complicate treatment (10, 11). Up to 50% of the patients are non-compliant to the medication (12). Lack of insight may cause refusal of receiving antipsychotic medications, leading to failure of initiation or continuation of therapy and worsening of the outcome (13). Involuntary treatment may thus be warranted to avert risk of suicide, treating a life-threatening medical condition, aggressiveness or to facilitate insight into the disease, to consequently accept the necessity of treatment. Especially, substance abuse, lack of insight and male sex seems to increase the risk of involuntary admission (14–16).

The use of involuntary treatment in psychiatry is highly controversial and has been extensively debated (15, 17–19). Essential of this discussion is the issue of loss of autonomy versus necessity of treatment both from society and patient's health points of view.

Furthermore, involuntary treatment may keep patients from seeking proper treatment later on (20).

In Denmark involuntary treatment is governed by the Mental Health Act. All involuntary interventions are registered on specified coercive protocols and reported electronically to a nation-wide register. Involuntary treatments are restricted to inpatient status. Continuation during outpatient status thus is not allowed, and consequently effectiveness of the involuntary treatment is pending on the patients gaining insight into their disease during treatment, thereby possibly gaining a more positive attitude and larger acceptance of the needed medications.

In Denmark, involuntary treatment is divided in two different groups and registered on two different coercive protocols. Involuntary treatment involving treatment of psychosis or a life-threatening medical condition (Coercive Protocol 2) compared with rapid tranquilization used for treating severe agitation in the emergency settings (Coercive Protocol 3). The Coercive Protocol is the piece of paper where the psychiatrist documents the involuntary measure. Each type of involuntary measure has a specific protocol reflecting the different clauses in the Mental Health Act. Measures governed by Coercive Protocol 3 can only be used once per protocol, whereas involuntary treatment by Coercive Protocol 2 makes it possible to apply the treatment once or several times per day until the condition has been cured or the patient accepts the treatment.

Rapid tranquilization can be applied by any doctor in the psychiatric ward were as involuntary treatment (Coercive Protocol 2) warrants accept from a psychiatric consultant. Only well-known drugs are permitted, and dosage should be within the recommended dose range. The use of involuntary treatment should always be proportionate to the goal pursued. Whenever possible, minor steps should be taken and accordingly involuntary treatment is divided in two measures: The main and the subsidiary treatment. The main treatment is less intrusive for the patient and usually is an orally administered drug, that is, tablets, orally disintegrating tablets or draught. If completing the main treatment is not possible, for example the patient refuses to take the tablets, the subsidiary treatment is used, usually an injectable drug. Long-acting depot antipsychotics only are allowed under certain circumstances, such as recurring discontinuation of treatment with relapse.

In life-threatening conditions the Mental Health Act permits specific involuntary measures, such as electroconvulsive therapy (ECT) or specific and necessary treatment of physical disease. Treatments of life-threatening physical disease warrant accept from both a psychiatric and a somatic consultant.

All patients subjected to involuntary measures are offered the assistance of a patient counsellor, through which patients may complain, and for the exception of life-threatening conditions, or severe violence, treatment is postponed until approved by the Patients' Complaints Board. Rapid tranquilization does not warrant approval by Patients' Complaints Board but patients can complain afterwards. Obtaining sufficient treatment in schizophrenia and avoiding relapse is considered

important and may even improve the long-term outcome of the disease (2, 21). Little, however, is known about involuntary treatment.

Aims of the study

This study aims to enlighten current practice by analysing types of treatment, the kind of drugs used, as well as their dosage.

Material and methods

Sample and registers

The population consisted of patients alive in the period 2004–2010 with a lifetime diagnosis of Schizophrenia (ICD10 F20.0–9). Patients were identified in the Danish Psychiatric Central Research Register (DPCRR) (22). The DPCRR contains information of all psychiatric admissions from 1969 and outpatient contacts from 1995 and onwards. The DPCRR has extensively been used for research and the validity is high (2, 23). Data were linked to The Registry of Coercive Measures in Psychiatric Treatment using the unique personal ID number. The reporting is based on paper protocols until January 01 2005; afterwards, the reporting is done electronically from the hospitals. The registry contains information on all involuntary measures from all psychiatric hospitals in Denmark. Only involuntary measures initiated during the study period where included. The National Health Service, Statistics Denmark and The Danish Data Protection Agency approved the use of the data for the study. Data were accessed anonymously through a remote access to Statistics Denmark.

Outcome variables

This study includes two measures, involuntary treatment of psychosis or medical condition (Coercive Protocol 2) and rapid tranquilization (Coercive Protocol 3). Drugs used for rapid tranquilization were not specified on the protocol, and for this reason only incidence rates could be reported. Coercive Protocol 2 includes a text string named 'type and volume'. This text string was deciphered into following variables: drug name, start and end dose. All of these variables were coded for both the main and the subsidiary treatment. Psychotropics were coded by their Anatomical Therapeutic Class (ATC) code, and classes of psychotropics were defined as: antipsychotics (N05A except N05AN01), antidepressants (N06A), stimulants (N06B), benzodiazepines (N03AE01 & N05BA), anticholinergic (N04A) and mood stabilizers including lithium (N05AN01), valproate (N03AG01), carbamazepine (N03AF01) and lamotrigine (N03AX09).

The recommended dose range for each antipsychotic drug was identified from the Danish summary of product characteristics (SPC), which was obtained from either the Danish Medicines Agency or European Medicines Agency. This was carried out to calculate the number of patients and percentage of those receiving higher dosages than the recommended range. Treatment including more than one psychotropic was registered as polypharmacy, and each drug was included in the table. Thus, the total number of drugs used exceeds the number of involuntary treatments.

For patients having more than one involuntary treatment, demographic data were registered during their first period. Demographics and treatment history were compared with patients not undergoing involuntary treatment or rapid tranquilization within the study period. For these controls, the index time was set to their first psychiatric admission within the study period, to calculate (e.g.) numbers of previous admissions and duration of illness.

For other analyses than demographics, all episodes of involuntary treatment within the study period were used in the analysis. Types of somatic treatment were manually categorized in relevant types of treatment.

Statistics

Statistical calculations were taken with STATA version 12.0. Mean values were compared, using unpaired student t-test. In case of non-normal distribution, the variables were transformed. Binary variables were compared by chi-squared test.

Only double-sided test results were reported and only *P*-values less than 0.05 were considered statistically significant. Observation time for incidence rate analysis were defined as from 0 to 1st of January 2004 or onset of schizophrenia if later, until death or end of register 31 December 2010 whichever came first. Incidence rates were reported for multiple episodes, that is patients with more than one episode had all episodes included in the analysis.

Results

Descriptive analysis

During the study period, a total of 34 898 people had a lifetime diagnosis of schizophrenia, and 18 599 had at least one psychiatric admission

within the study period and were considered the study population.

In total 3078 patients (16.5%) of the admitted patients underwent involuntary treatment or rapid tranquilization. Total number of registrations of rapid tranquilization was 16 364 by 2574 patients (median 2.0 treatments per person 25–75 percentiles 1–6; range, 1–270). Corresponding figure of involuntary treatment was 3151 treatments by 1384 patients (median 1 treatment per person, 25–75 percentiles 1–2, range 1–35). Eight hundred and eighty patients had both at least one episode of rapid tranquilization and one involuntary treatment.

The total observation time was 195 929 patient years with 9363 in-patient years. The incidence rate for any involuntary treatment was 2.1 per in-patient year and 1.7 and 0.3 per in-patient year for rapid tranquilization and involuntary treatments, respectively. Demographics of patients subjected to any involuntary treatment vs. admitted patients not receiving involuntary treatment are shown in Table 1. Patients undergoing involuntary treatment were younger, with earlier onset of both schizophrenia and any psychiatric disease, and more prior psychiatric admissions compared with admitted patients not receiving involuntary treatment as shown in Table 1.

Psychotropics comprised 56.9% of all involuntary treatments as shown in Table 2. Mean number of times the medication was administered involuntarily was 27 (25–75 percentiles 8–61, range, 0–822) times. Electroconvulsive therapy, of which 25% was given 'en bloc' (daily treatment for three consecutive days, bilaterally), comprised 4.8% of all involuntary treatments.

In 18% per cent of the protocols, data were blank or insufficiently registered, meaning the description in the protocol was not explicit enough for anyone else but the physician himself to decipher what treatment to be administered.

Table 1. Demographics of admitted schizophrenia patients

	No involuntary treatment (N = 15 521)	Any involuntary treatment (N = 3078)	P-value
Male sex	8 967 (57.8%)	1777 (57.7%)	0.96
Age (years)	38.7 (SD = 15.5)	34.4 (SD = 11.7)	<0.001
Age at first psychiatric contact (years)	28.1 (SD = 11.0)	24.4 (SD = 8.3)	<0.001
Age at onset of schizophrenia (years)	33.0 (SD = 12.7)	29.0 (SD = 13.1)	<0.001
Duration of psychiatric illness (years)	12.9 (SD = 11.6)	12.5 (SD = 9.9)	0.038
Duration of schizophrenia (years)	10.6 (SD = 10.6)	9.3 (SD = 8.6)	<0.001
Number of previous psychiatric admissions (#, 25–75 percentiles)	4 (0–11)	7 (2–17)	<0.001
Percentage of hospitalization during course of schizophrenia (percentage, 25–75 percentiles)	5.6 (1.2–15.2)	10.0 (2.6–23.7)	<0.001
Time from hospitalization to decision on involuntary treatment (days)	–	6.1 (SD = 20.0)	–

Table 2. Types of involuntary treatment (Coercive Protocol 2).

	Total	Subtotal
Total	3151 (100.0%)	
Any kind of ECT	152 (4.8%)	
ECT		114 (75.0%)
ECT-en bloc		38 (25.0%)
Somatic treatment/procedures	640 (20.3%)	
Acetaminophen overdose		151 (23.6%)
Antibiotics		29 (4.5%)
Anticoagulant therapy		30 (4.7%)
Blood sampling		37 (5.8%)
Blood transfusion		6 (0.9%)
Compulsory Feeding		109 (17.0%)
Diagnostic imaging		6 (0.9%)
Fluid replacement therapy		46 (7.2%)
Gastroscopy		8 (1.3%)
Insulin		24 (3.8%)
Surgical		46 (7.2%)
Treatment of withdrawal symptoms		9 (1.4%)
Other overdose		63 (9.8%)
Other/unspecified		76 (11.9%)
Psychotropics*	1792 (56.9%)	
Antipsychotics		1783 (99.5%)
Antidepressants		9 (0.5%)
Mood stabilizers		11 (0.6%)
Benzodiazepines		38 (2.1%)
Anticholinergic		87 (4.9%)
Stimulants		0 (0.0%)
Unsatisfied filled out	567 (18.0%)	
Blank		512 (90.3%)
Lack of information		55 (9.7%)

*The total percentage of the individual drug groups is higher than 100% because some patients are treated with polypharmacy.

Involuntary psychopharmacological treatment

Antipsychotics comprised 99.5% of all involuntary treatments involving psychotropics as shown in Table 2. Olanzapine was the most commonly administered antipsychotic drug (33.2%) (cf. table 3). Of the 1792 involuntary treatments, 163 (9.1%) treatments included polypharmacy. Antipsychotic polypharmacy comprised 46 (28.2%) of the total number of treatments involving polypharmacy. Other combinations of polypharmacy were antipsychotic + anticholinergic 87 (53.4%), antipsychotic + benzodiazepines 38 (23.3%) and antipsychotic + moodstabilizer 10 (6.1%).

In total 203 involuntary treatments (13.0%) involved long-acting depot injections

Table 3. Antipsychotic drugs used in involuntary treatment

	#	Mean maximum dose	Above recommended dose	Maximum allowed dose
Oral				
Amisulpride	10	711.1 (SD = 318.0)	0 (0.0%)	1200 mg
Aripiprazole	116	23.8 (SD = 10.3)	6 (5.2%)	30 mg
Chlorprothixene	8	87.5 (SD = 44.3)	0 (0.0%)	600 mg
Clozapine	85	430.9 (SD = 246.9)	0 (0.0%)	900 mg
Flupenthixol	10	22.8 (SD = 14.8)	0 (0.0%)	40 mg
Levomepromazine	5	215.0 (SD = 230.2)	1 (20.0%)	300 mg
Haloperidol	104	17.9 (SD = 10.8)	7 (6.7%)	30 mg
Olanzapine	449	27.7 (SD = 15.6)	197 (43.9%)	20 mg
Paliperidone	10	8.3 (SD = 3.3)	0 (0.0%)	12 mg
Perphenazine	44	26.3 (SD = 13.8)	0 (0.0%)	64 mg
Quetiapine	86	754.6 (SD = 352.6)	23 (26.7%)	800 mg
Risperidone	330	5.7 (SD = 3.0)	0 (0.0%)	16 mg
Sertindole	13	15.6 (SD = 6.4)	0 (0.0%)	24 mg
Sulpiride	1	1800.0 (SD = -)	0 (0.0%)	1800 mg
Ziprasidone	54	166.1 (SD = 65.1)	11 (22.4%)	160 mg
Zuclopenthixol	226	28.8 (SD = 15.8)	19 (8.4%)	40 mg
Injection				
Aripiprazole	144	15.3 (SD = 8.6)	0 (0.0%)	29.3 mg
Clozapine	2	350.0 (SD = 70.7)	0 (0.0%)	900 mg
Levomepromazine	10	11.3 (SD = 204.9)	–	–
Haloperidol	310	11.1 (SD = 8.1)	8 (3.1%)	30 mg
Olanzapine	503	15.7 (SD = 9.5)	35 (7.6%)	20 mg
Ziprasidone	145	34.4 (SD = 32.7)	14 (10.4%)	40 mg
Zuclopenthixol	137	16.8 (SD = 9.1)	0 (0.0%)	80 mg
Depot injection				
Flupenthixol decanoate	5	120.0 (SD = 75.8)	0 (0.0%)	200 mg/2w
Haloperidol decanoate	47	262.2 (SD = 62.3)	30 (66.7%)	200 mg/2w
Olanzapine pamoate	11	338.2 (SD = 53.0)	0 (0.0%)	450 mg/2w
Perfenazine decanoate	24	180.7 (SD = 99.8)	0 (0.0%)	400 mg/2w
Risperidone long acting	93	53.1 (SD = 17.6)	23 (26.7%)	50 mg/2w
Zuclopenthixol acetate	87	93.3 (SD = 41.4)	1 (1.3%)	225 mg/3d
Zuclopenthixol decanoate	86	263.9 (SD = 147.3)	5 (6.5%)	400 mg/2w

(zuclopenthixol acetate not included). Especially for olanzapine, quetiapine and ziprasidone large portion of the oral treatment exceeded the maximum recommended dose.

Pharmaceutical form

Solid tablets were most commonly administered for main treatment, whereas short-acting injection was the most common for the subsidiary treatment (cf. Table 4.) Other orally administered pharmaceutical forms were also commonly administered for the main treatment, that is orally disintegrating tablets (22.2%) and draught (16.5%). Gastric tubes were used in less than 1% of cases for both main and subsidiary treatment and were mainly used for clozapine treatment.

Table 4. Pharmaceutical form used for involuntary treatment with psychotropics

	Main		Subsidiary	
	#	%	#	%
Tablets	770	43.0	42	3.1
Draught	295	16.	15	1.1
Oral disintegrating tablets	397	22.2	9	0.7
Injection	73	4.1	1200	87.5
Injection depot	234	13.1	32	2.3
Zuclopenthixol acetate	17	1.0	70	5.1
Gastric tube	6	0.3	4	0.3
Total	1792	100.0	1372	100.0

Discussion

This is the first study to ever investigate involuntary treatment of schizophrenia patients in Denmark. Treatment with psychotropics comprised only 56.9% of the total number of involuntary treatments. Somatic involuntary measures thus comprised 20.3%, overdose being the most frequent somatic condition. Somatic involuntary treatment included a wide variety of conditions from minor interventions, for example rehydration, or more severe interventions such as amputation of limbs.

The average age of patients who have been undergoing involuntary treatment was mid-thirties as found in a previous study by Jarrett (11). Although more males underwent involuntary treatment, their relative proportion was similar to admitted patients not undergoing involuntary treatment. Patients with earlier onset of schizophrenia were more likely to have involuntary treatment, which may be explained by the poorer outcome of this patient group (24).

Antipsychotics, as expected, comprised the most frequent class of drugs for involuntary treatment in this patient group. Olanzapine was the atypical antipsychotic drug most frequently used, in consistence with general use of antipsychotics (25). The relatively high numbers, in involuntary treatment, of zuclopenthixol, olanzapine and haloperidol may reflect the fact that parenteral route of administration is available for these drugs.

For olanzapine 44% and quetiapine, 27% of the patients received higher than recommended dosages. Such is controversial in involuntary treatment where patients do not have the option to refuse the treatment and because of the current legislation. In addition, treatments including more than one psychotropic comprised 9.1% of all treatments. Evidence for beneficial effects from doses above the recommended range, as well as from polypharmacy, remains sparse (26). In treatment resistant cases clozapine is a more evidence-based

alternative (26, 27) and a previous study has documented its feasibility, safety and effectiveness as involuntary treatment (28). Still only 85 (4.8%) involuntary treatments involved clozapine even though clozapine remains the drug of choice for treatment resistant schizophrenia, thus in most treatment, guidelines recommended as the drug of choice following failure of two or three antipsychotic drugs (26, 29, 30).

In general, psychiatrists seem reluctant to prescribe clozapine, and even more so in involuntary treatment, considering the relative chronicity in this group of patients (31, 32). One reason may be fear of serious side effects, another the necessity of haematological monitoring (33). The unavailability of clozapine as an injectable drug also may prevent psychiatrists from prescribing clozapine for involuntary treatment.

The unique effect of clozapine, including higher level of insight into the disease and thereby longer time to discontinuation (34), may call for prescription of clozapine after non-response to two or three different antipsychotics, even when involuntary treatment is warranted. Involuntary treatment with clozapine should be practicable using a stomach tube or having injectable clozapine manufactured.

Several of the atypical short-acting injectable drugs are only licensed for three consecutive days which often led to alternation between two kinds of injectable antipsychotics. From a pharmacological point of view, this is inappropriate and future studies investigating the safety of injectable antipsychotics beyond three days should be carried out.

Electroconvulsive therapy (ECT) comprised almost 5% of all involuntary treatments, which is rather high based on the sparse evidence for ECT in patients with schizophrenia (35). Unfortunately, indication for ECT or description of symptoms was not available. However, some evidence exists for treatment refractory schizophrenia, catatonic symptoms and from acute relapse when a more rapid improvement is desired (35, 36).

Only 13% of the involuntary treatment (main treatment) included depot injection. In involuntary treatment, long-acting antipsychotics have several advantages. Depot injections every 2–4 weeks should be less stressful for patients, objecting to medicine, compared with daily injections or tablets. Also, in general, the amount of time before discontinuation is higher for treatment with depot injections compared with oral treatment (37). Thirdly, avoiding parenteral depot medication by coercion is not possible, because oral medications patients can easily cheat (38). On the downside, the palettes of parenteral atypical antipsychotics depots remain limited, but the availability may increase in the future.

More studies are warranted to investigate the effects of involuntary treatment with depot injections, and legislators should be aware of the potential effect of such interventions on compliance and course.

This study should be interpreted within its limitations. A large portion of the protocols was not sufficiently completed or blank, which could be due to lack of reporting. Regarding involuntary somatic treatment, data and description often were wide and non-specific (e.g. 'treatment of physical disease') containing no information on drug or dosage. Indications for psychotropics were not available, which frequently makes it impossible to distinguish, for instance, whether antiepileptics are used for seizure control or mood stabilizing. Unfortunately, drugs used for rapid tranquilization were not specified in the protocol.

Comparing this study to other studies is restricted because of the lack of existing literature within this field and international differences in mental health acts and procedures of involuntary treatment. Most studies have investigated the effects of involuntary community treatment, which was not allowed during in Denmark during the study period (39). One study investigating the short-term effect of involuntary treatment during hospitalization revealed that no differences at time of discharge as regards to psychopathology and level of functioning (40). Since lack of insight is an important risk factor for non-adherence and involuntary admission, psychiatrists should aim for remission of psychotic symptoms, try to involve the patient in decision making and provide psychoeducation to increase the patient's level of insight into the disease and thereby increase the likelihood of continuing treatment after discharge (41).

A Cochrane study concluded that compulsory community treatment did not result in any significant difference in service use, social functioning or quality of life patients sentenced to involuntary community treatment compared with standard care, although they were less likely to be involved in serious crime (39). Other studies have concluded that involuntary out-patient treatment is effective and can easily be managed with rarely use of physical force (42). Our study only aimed to describe current use of involuntary treatment among schizophrenia inpatients and thus further investigation of the long-term effects, both as regards to compliance and to the psychological effects is beyond its scope.

In conclusion, 16.5% of all psychiatric admitted patients with schizophrenia during a 7-year study

period underwent involuntary treatment. More studies investigating involuntary treatment is warranted to obtain knowledge on feasibility of involuntary treatment and the outcome of such treatment.

Declaration of interest

J. Nielsen has received research grants from H. Lundbeck, Pfizer and Chempaq for clinical trials and received speaking fees from Bristol-Myers Squibb, Astra Zeneca, Lundbeck, Janssen–Cilag, Hemocue, and Eli-Lilly. Other authors report no conflict of interest.

References

1. Ingason A, Giegling I, Cichon S, et al. A large replication study and meta-analysis in European samples provides further support for association of AHI1 markers with schizophrenia. Hum Mol Genet 2010;**19**:1379–1386.
2. Uggerby P, Nielsen RE, Correll CU, Nielsen J. Characteristics and predictors of long-term institutionalization in patients with schizophrenia. Schizophr Res 2011;**131**:120–126.
3. Lang FU, Kosters M, Lang S, Becker T, Jager M. Psychopathological long-term outcome of schizophrenia - a review. Acta Psychiatr Scand 2013;**127**:173–182.
4. Breslau J, Miller E, Jin R, et al. A multinational study of mental disorders, marriage, and divorce. Acta Psychiatr Scand 2011;**124**:474–486.
5. Bennett DJ, Ogloff JR, Mullen PE, Thomas SD, Wallace C, Short T. Schizophrenia disorders, substance abuse and prior offending in a sequential series of 435 homicides. Acta Psychiatr Scand 2011;**124**:226–233.
6. Hoang U, Goldacre MJ, Stewart R. Avoidable mortality in people with schizophrenia or bipolar disorder in England. Acta Psychiatr Scand 2013;**127**:195–201.
7. Palmer BA, Pankratz VS, Bostwick JM. The lifetime risk of suicide in schizophrenia: a reexamination. Arch Gen Psychiatry 2005;**62**:247–253.
8. Vancampfort D, Knapen J, Probst M, Scheewe T, Remans S, de Hert M. A systematic review of correlates of physical activity in patients with schizophrenia. Acta Psychiatr Scand 2012;**125**:352–362.
9. Nielsen J, Munk-Jorgensen P, Skadhede S, Correll CU. Determinants of poor dental care in patients with schizophrenia: a historical, prospective database study. J Clin Psychiatry 2011;**72**:140–143.
10. Mohamed S, Rosenheck R, McEvoy J, Swartz M, Stroup S, Lieberman JA. Cross-sectional and Longitudinal Relationships Between Insight and Attitudes Toward Medication and Clinical Outcomes in Chronic Schizophrenia. Schizophr Bull 2009;**35**:336–346.
11. Jarrett M, Bowers L, Simpson A. Coerced medication in psychiatric inpatient care: literature review. J Adv Nurs 2008;**64**:538–548.
12. Gutierrez-Casares JR, Canas F, Rodriguez-Morales A, Hidalgo-Borrajo R, Alonso-Escolano D. Adherence to treatment and therapeutic strategies in schizophrenic patients: the ADHERE study. CNS Spectr 2010;**15**:327–337.
13. Jonsdottir H, Opjordsmoen S, Birkenaes AB, et al. Predictors of medication adherence in patients with schizophrenia and bipolar disorder. Acta Psychiatr Scand 2013;**127**:23–33.
14. Opsal A, Clausen T, Kristensen O, Elvik I, Joa I, Larsen TK. Involuntary hospitalization of first-episode psychosis with substance abuse during a 2-year follow-up. Acta Psychiatr Scand 2011;**124**:198–204.
15. Cougnard A, Kalmi E, Desage A, et al. Factors influencing compulsory admission in first-admitted subjects with psychosis. Soc Psychiatry Psychiatr Epidemiol 2004;**39**:804–809.
16. Montemagni C, Bada A, Castagna F, et al. Predictors of compulsory admission in schizophrenia-spectrum patients: excitement, insight, emotion perception. Prog Neuropsychopharmacol Biol Psychiatry 2011;**35**:137–145.
17. Steinert T, Lepping P, Baranyai R, Hoffmann M, Leherr H. Compulsory admission and treatment in schizophrenia: a study of ethical attitudes in four European countries. Soc Psychiatry Psychiatr Epidemiol 2005;**40**:635–641.
18. Nordt C, Rossler W, Lauber C. Attitudes of mental health professionals toward people with schizophrenia and major depression. Schizophr Bull 2006;**32**:709–714.
19. Lauber C, Nordt C, Falcato L, Rossler W. Public attitude to compulsory admission of mentally ill people. Acta Psychiatr Scand 2002;**105**:385–389.
20. Swartz MS, Swanson JW, Hannon MJ. Does fear of coercion keep people away from mental health treatment? Evidence from a survey of persons with schizophrenia and mental health professionals. Behav Sci Law 2003;**21**:459–472.
21. Nielsen J, Nielsen RE, Correll CU. Predictors of clozapine response in patients with treatment-refractory schizophrenia: results from a Danish Register Study. J Clin Psychopharmacol 2012;**32**:678–683.
22. Mors O, Perto GP, Mortensen PB. The Danish Psychiatric Central Research Register. Scand J Public Health 2011;**39**:54–57.
23. Munk-Jorgensen P, Ostergaard SD. Register-based studies of mental disorders. Scand J Public Health 2011;**39**:170–174.
24. Hollis C. Adult outcomes of child- and adolescent-onset schizophrenia: diagnostic stability and predictive validity. Am J Psychiatry 2000;**157**:1652–1659.
25. Nielsen J, le Quach P, Emborg C, Foldager L, Correll CU. 10-Year trends in the treatment and outcomes of patients with first-episode schizophrenia. Acta Psychiatr Scand 2010;**122**:356–366.
26. Barnes TR. Evidence-based guidelines for the pharmacological treatment of schizophrenia: recommendations from the British Association for Psychopharmacology. J Psychopharmacol 2011;**25**:567–620.
27. Taylor DM, Smith L, Gee SH, Nielsen J. Augmentation of clozapine with a second antipsychotic - a meta-analysis. Acta Psychiatr Scand 2012;**125**:15–24.
28. Schulte PF, Stienen JJ, Bogers J, et al. Compulsory treatment with clozapine: a retrospective long-term cohort study. Int J Law Psychiatry 2007;**30**:539–545.
29. Nielsen J, Damkier P, Lublin H, Taylor D. Optimizing clozapine treatment. Acta Psychiatr Scand 2011;**123**:411–422.
30. Buchanan RW, Kreyenbuhl J, Kelly DL, et al. The 2009 schizophrenia PORT psychopharmacological treatment recommendations and summary statements. Schizophr Bull 2010;**36**:71–93.
31. Nielsen J, Roge R, Schjerning O, Sorensen HJ, Taylor D. Geographical and temporal variations in clozapine prescription for schizophrenia. Eur Neuropsychopharmacol 2012;**22**:818–824.

32. Nielsen J, Dahm M, Lublin H, Taylor D. Psychiatrists' attitude towards and knowledge of clozapine treatment. J Psychopharmacol 2010;**24**:965–971.
33. Nielsen J, Foldager L, Meyer JM. Increased use of antibiotics in patients treated with clozapine. Eur Neuropsychopharmacol 2009;**19**:483–486.
34. McEvoy JP, Lieberman JA, Stroup TS, et al. Effectiveness of clozapine versus olanzapine, quetiapine, and risperidone in patients with chronic schizophrenia who did not respond to prior atypical antipsychotic treatment. Am J Psychiatry 2006;**163**:600–610.
35. Tharyan P, Adams CE. Electroconvulsive therapy for schizophrenia. Cochrane Database Syst Rev 2005: CD000076.
36. Chanpattana W, Kramer BA. Acute and maintenance ECT with flupenthixol in refractory schizophrenia: sustained improvements in psychopathology, quality of life, and social outcomes. Schizophr Res 2003;**63**:189–193.
37. Adams CE, Fenton MK, Quraishi S, David AS. Systematic meta-review of depot antipsychotic drugs for people with schizophrenia. Br J Psychiatry 2001;**179**:290–299.
38. Agid O, Foussias G, Remington G. Long-acting injectable antipsychotics in the treatment of schizophrenia: their role in relapse prevention. Expert Opin Pharmacother 2010;**11**:2301–2317.
39. Kisely S, Campbell LA, Preston N. Compulsory community and involuntary outpatient treatment for people with severe mental disorders. Cochrane Database Syst Rev 2005;**123**:CD004408.
40. Steinert T, Schmid P. Effect of voluntariness of participation in treatment on short-term outcome of inpatients with schizophrenia. Psychiatr Serv 2004;**55**:786–791.
41. Hamann J, Mendel RT, Fink B, Pfeiffer H, Cohen R, Kissling W. Patients' and psychiatrists' perceptions of clinical decisions during schizophrenia treatment. J Nerv Ment Dis 2008;**196**:329–332.
42. Pinfold V, Bindman J, Thornicroft G, Franklin D, Hatfield B. Persuading the persuadable: evaluating compulsory treatment in England using Supervised Discharge Orders. Soc Psychiatry Psychiatr Epidemiol 2001;**36**:260–266.